Myocardial Infarction With Angiographically Normal Coronary Arteries*

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To determine the prevalence rate and clinical and hemodynamic profile of patients with myocardial infarction (MI) with angiographically normal coronary arteries, we analyzed 3,403 consecutive angiograms performed within a 4.5-year period. Of these studies, 1,124 were performed following an acute MI. Through a computerized search, 12 patients were identified who had documented MI with normal or insignificant (<30% stenosis in one epicardial vessel only) coronary disease. Q-wave MI developed in five patients (group A) and non-Q-wave MI developed in seven patients (group B). Group A patients were all men whereas group B patients were all women. Overall, group A patients were younger (p=0.003), had a longer smoking history (p=0.008), and a higher cardiac index (p=0.005). In ten patients, areas of localized dyskinesia or hypokinesia were shown on left ventricular cineangiography. Mitral valve prolapse was present in four of the patients and varying degrees of mitral regurgitation were identified in another six. The prevalence rate of MI with angiographically normal coronary arteries was 1% in this study. This entity had a bimodal age and sex distribution: a younger age group, all men, with a stronger cigarette smoking history who had Q-wave MI vs an older age group, all women, and no significant association with cigarette smoking who developed non-Q-wave MI. A mean follow-up of 4 years demonstrated a favorable prognosis in both groups.

Key words: coronary angiography; coronary artery disease; mitral regurgitation; mitral valve prolapse; myocardial infarction

Myocardial infarction (MI) is most commonly due to the development of arterial thrombosis superimposed on an atherosclerotic epicardial coronary artery. The pathophysiologic state of MI involves an intricate and complex interaction among the atherosclerotic plaque, thrombus formation, coronary vasospasm, and platelet activation. With the advent of selective coronary angiography, it has been well recognized that MI may occur in the presence of angiographically normal coronary arteries. Proposed mechanisms include coronary artery spasm, thrombosis with spontaneous thrombolysis, embolization with recanalization, cocaine abuse, and viral myocarditis. Other factors incriminated in the pathogenesis of MI without significant fixed coronary obstruction include chest trauma, aortic dissection, hypercoagulable states, autoimmune vasculitis, and carbon monoxide intoxication. The prevalence rate of MI with normal or near normal coronary arteries varies from 1 to 12% depending on the study population and definition of a "normal" or "near normal" angiogram. The overall prognosis in these patients is favorable. The annual incidence of death is about 1.5% and that of recurrent MI is 2.7%.

The purpose of the present study was to describe our experience with patients who had an acute MI in the presence of a normal coronary angiogram. The clinical, hemodynamic, and demographic characteristics are discussed and the short- and long-term outcome is described.

Materials and Methods

Between August 1987 and January 1992, 3,403 consecutive coronary angiograms were performed in our institution, of which 1,124 followed an acute MI. Of these, 12 patients were identified through a computerized search and had a documented MI with angiographically normal coronary arteries. A normal angiogram was defined as a study with no intraluminal irregularities (seven patients) or with a single lesion with less than 30% narrowing in the luminal diameter in only one of the major epicardial vessels (five patients). The patients' previous quantitative catheterization reports were used to assess the severity of stenosis. The clinical, hemodynamic, and pertinent data of these 12 patients were reviewed.

At the time of hospital admission, all patients had acute chest pain with ECG changes and a rise in serum creatinine phosphokinase, MB fraction, and lactate dehydrogenase levels. A Q-wave MI was considered present if in addition to chest pain and enzyme level elevation, the patient developed pathologic Q waves (Q/R amplitude >1/3 and Q wave duration >40 ms) with hyperacute ST segment elevation and symmetrical T-wave inversions that underwent typical evolution. The diagnosis of non-Q-wave MI was made if the ECG showed persistent ischemic
Table 1—Selected Clinical and Hemodynamic Findings*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ECG Site of MI</th>
<th>Peak CPK, U/L</th>
<th>CI, L/min/m²</th>
<th>LVgram</th>
<th>Mitral Valve Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/46</td>
<td>Inferior</td>
<td>3,050</td>
<td>3.62</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>2/33</td>
<td>Anterolateral</td>
<td>3,390</td>
<td>4.1</td>
<td>Akinetic: anterolateral</td>
<td>MVP</td>
</tr>
<tr>
<td>3/44</td>
<td>Anterior</td>
<td>267</td>
<td>2.9</td>
<td>Hypokinetic: inferior and apical</td>
<td>MVP</td>
</tr>
<tr>
<td>4/31</td>
<td>Inferior</td>
<td>2,989</td>
<td>2.2</td>
<td>Hypokinetic: anterolateral</td>
<td>MR grade 1</td>
</tr>
<tr>
<td>5/40</td>
<td>Inferior</td>
<td>477</td>
<td>3.4</td>
<td>Hypokinetic: inferior</td>
<td>MR grade 2</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/42</td>
<td>Anterolateral</td>
<td>210</td>
<td>2.0</td>
<td>Hypokinetic: anterolateral and apical</td>
<td>MR grade 2</td>
</tr>
<tr>
<td>7/68</td>
<td>Anterior</td>
<td>235</td>
<td>2.9</td>
<td>Hypokinetic: apical</td>
<td>MVP†</td>
</tr>
<tr>
<td>8/61</td>
<td>Inferior</td>
<td>494</td>
<td>2.0</td>
<td>Hypokinetic: inferior and diaphragmatic</td>
<td>MR grade 1</td>
</tr>
<tr>
<td>9/67</td>
<td>Septal</td>
<td>179</td>
<td>1.8</td>
<td>Hypokinetic: apical and septal</td>
<td>—</td>
</tr>
<tr>
<td>10/73</td>
<td>Inferior</td>
<td>240</td>
<td>1.7</td>
<td>Hypokinetic: anterolateral</td>
<td>MR grade 3†</td>
</tr>
<tr>
<td>11/56</td>
<td>Anterolateral</td>
<td>210</td>
<td>2.1</td>
<td>Akinetic: anterolateral</td>
<td>MR grade 2</td>
</tr>
<tr>
<td>12/53</td>
<td>Inferior</td>
<td>360</td>
<td>2.0</td>
<td>Hypokinetic: inferior</td>
<td>MVP</td>
</tr>
</tbody>
</table>

*CI=cardiac index; MR=mitral regurgitation; MVP=mitral valve prolapse; CPK=creatine phosphokinase; LVgram=left ventriculogram.
†Patent foramen ovale.
‡Chronic atrial fibrillation due to rheumatic heart disease.

T waves or ST segment depression lasting longer than 48 h without subsequent development of Q waves. These patients also had chest pain at the time of hospital admission with positive enzymes but no elevation of the ST segment. Q-wave MI developed in five patients (group A) and non-Q-wave MI developed in seven patients (group B). All patients underwent catheterization of the left and right sides of the heart, left ventriculography, and cineangioigraphy of the coronary arteries in multiple projections within the same hospitalization ranging from 2 to 11 days after the acute episode. Angiography was performed primarily because of the young age of the patients in group A and presence of residual angina and the non-Q-wave nature of MI in group B. Contrast left ventriculography was used to assess the severity of mitral regurgitation and the presence of mitral valve prolapse. If a jet of contrast agent entered the left atrium but cleared immediately, it was classified as grade 1, light atrial opacification as grade 2, atrial opacification equal to that of the ventricle as grade 3, and opacification of the atrium more than that of the ventricle as grade 4. Mitral valve prolapse was considered present if at end systole and 30° right anterior oblique view unequivocal protrusion of the posterior or anterior mitral leaflets into the left atrium was seen.

Follow-up was accomplished through telephone contact with these patients, their families, or physicians and ranged from 2.5 to 5 years.

Statistical Analysis

Data are presented as means ± SE. Comparisons between continuous variables were done using the two-tailed t test. A p value of <0.05 was considered statistically significant.

RESULTS

The clinical data and selected hemodynamic findings are shown in Table 1. By definition, all Q wave MIs occurred in group A and all non-Q-wave MIs occurred in group B. Interestingly, all group A patients were men whereas all group B patients were women.

Initial Course

Premature ventricular contractions developed in three patients of group A and in one patient of group B. In addition, one of the above patients (case 2) developed nonsustained monomorphic ventricular tachycardia. All of these patients were treated with lidocaine. One patient in group A developed third-degree atrioventricular block requiring a pacemaker and two patients in group B developed congestive heart failure and were treated with furosemide. Three days after MI, one patient developed residual angina that was self-limited and not associated with ECG changes. There was no predilection for a specific location of MI on the basis of ECG criteria. None of the patients received thrombolytic therapy. An effort was made to study the recognized potential risk factors associated with atherosclerotic coronary artery disease. All patients in group A were smokers and had a significantly higher pack-year history (Table 2). One patient in group A (case 3) gave a history of cocaine and marijuana abuse. In this patient, cocaine was detected in his urine at the time

Table 2—Comparison of Selected Clinical and Hemodynamic Data Between the Two Groups*

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>38.8 (2.98)</td>
<td>60 (4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cigarettes, pack-year</td>
<td>25 (5.02)</td>
<td>1.86 (1.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak CPK, U/L</td>
<td>2,034 (683)</td>
<td>275 (42)</td>
<td>0.061</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure, mm Hg</td>
<td>7.4 (1.5)</td>
<td>10.71 (1.76)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64.40 (4.06)</td>
<td>55.45 (6.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>3.24 (0.33)</td>
<td>2.07 (0.15)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Values denote mean (±SE). SE=standard error; CPK=creatine phosphokinase; NS=nonsignificant.
of hospital admission.

Hemodynamic Findings

In group A, left ventricular end-diastolic pressure was elevated in two patients, one of whom had a reduced ejection fraction (case 2). In group B, left ventricular end-diastolic pressure was elevated in three patients. Ejection fraction was depressed in two of these patients with definite decrease in cardiac index. Another patient (case 6) had reduced ejection fraction and cardiac index with a relatively lower left ventricular end-diastolic pressure. Overall, cardiac index was significantly higher in group A (p=0.005), whereas no statistical difference was noted in the ejection fraction and the mean pulmonary capillary wedge pressure between the two groups (Table 2).

Left ventricular cineangiography revealed some form of wall motion abnormality in ten patients. In general, there was a good correlation between the ECG location of MI and the angiographic findings.

Two patients in group A and two patients in group B had mitral valve prolapse. On transthoracic echocardiography, mitral valve prolapse was present in three of these patients. In the fourth patient, redundancy of the chordae tendineae with myxomatous thickening of the mitral valve was present. Mitral annular calcification was present in three patients in group B. An additional two patients in group A and four patients in group B had varying degrees of mitral regurgitation.

Follow-Up

A mean follow-up of 4 years on ten patients showed no mortality or recurrence of MI. All patients with the exception of patient 3 were placed on a regimen of aspirin. Diltiazem was given to group B patients except for patient 6 who received verapamil as she also had migraine headaches. Patients 7 and 9 had recurrence of chest pain 8 and 10 months after hospital discharge, respectively. Treadmill exercise tests performed at that time were normal.

DISCUSSION

Mechanisms of Infarction

Coronary atherosclerosis is the most common underlying disease in patients with MI. Coronary thrombosis superimposed on a fixed atherosclerotic plaque is usually the triggering event in the pathogenesis of MI. In the past two decades, several reports have documented the occurrence of MI in the presence of normal or near-normal coronary arteries. The prevalence of this entity has varied from 1% to 12%. In our patients, the prevalence rate was 1%. The reason for this apparent discrepancy is due to variation in the definition of a “normal” or “near-normal” angiogram and the number of vessels involved. To our knowledge, all studies involving both Q-wave and non-Q-wave MI have defined a near-normal angiogram as that with a stenosis of less than 50% or 75%. Our definition of a near-normal lesion has been stricter, i.e., less than 30% and limited to only one coronary artery. This may have accounted for the lower prevalence rate in our patients.

Coronary artery spasm has been implicated as a cause of MI with normal coronary arteries. Although shown to cause both chest pain and ischemic changes on ECG, the role of coronary spasm as a cause of myocardial necrosis has been questioned.

Perhaps the most plausible hypothesis is that of thromboembolism in one of the coronary arteries with subsequent lysis or recanalization of the occluding thrombus. Kereiakes et al described 42 patients with over 50% residual coronary stenosis 90 min after thrombolytic therapy and showed that the stenosis was reduced to less than 50% on repeated angiography 7 to 10 days later.

Platelet aggregates have been shown to produce severe myocardial ischemia and even transmural MI. Since platelet aggregates tend to have a short life span of 6 to 10 min, they may be incriminated as a cause of transient occlusion of the coronary vessel with subsequent disaggregation.

Coronary embolism may be implicated as a cause of MI and normal coronary arteries. It is often associated with valvular heart disease, endocarditis, mural thrombus, prosthetic valve disease, and left atrial myxoma. It could be postulated that a group of patients reported as having MI and normal coronary arteries may have had embolic MI with resolution of the emboli prior to angiography. In this study, three patients of group B had mitral annular calcification on echocardiography, a common finding in the elderly population. Whether mitral annular calcification may serve as an intracardiac source of emboli remains speculative.

In the present study, all Q-wave MIs occurred in young male patients who had a significant smoking history. These findings are consistent with the reports of some authors but differ from those of others. Cigarette smoking has been implicated in causing coronary thrombosis in patients through various mechanisms, including catecholamine release and coronary vasoconstriction. It has also been shown to disturb platelet function by increasing aggregation and adhesion of platelets to the endothelial lumen. Group B was composed of patients with non-Q-wave MI. Interestingly, they were all women and with one exception all were postmenopausal. Cigarette smoking was significantly less among these patients.
Close to 60% of our patients (7/12) had non-Q-wave MI. Only one other report in the literature has found similar results.\(^5\) Legrand et al\(^8\) showed a 61% incidence of subendocardial infarcts associated with normal coronary angiograms. In their series, all but one of the female patients had a subendocardial infarct and of these all were above the age of 40 years.\(^8\)

There was no predilection for the site of MI in any groups. This finding is consistent with the data of Raymond et al\(^{19}\) and Raizner and Chahine,\(^{11}\) but differs from the findings of others who have reported a higher prevalence of anterior wall involvement.\(^2,8\) Angiographic evidence of mitral valve prolapse was present in four patients: two from each group. Three of these patients had mitral valve prolapse diagnosed on echocardiography and the fourth patient had redundancy of the chordae tendineae and myxomatous thickening of the mitral leaflets but no prolapse. The sensitivity and specificity of mitral valve prolapse diagnosed on left ventriculography have been reported to be as high as 88% and 100%, respectively, when compared with transthoracic echocardiography.\(^20\) The association of mitral valve prolapse and MI with normal coronary arteries appears to be more than that expected by chance alone. Ciraulo et al\(^{21}\) reported a prevalence of 25% in patients who had sustained a transmural myocardial infarction and had normal coronary angiograms. A lower prevalence of 4% (but higher than controls) was described by Raymond et al.\(^{19}\) Interestingly, a similar association has been demonstrated between mitral valve prolapse and transient cerebral ischemic attacks suggesting a thromboembolic etiology.\(^{22}\) In addition, in this study, another six patients had variable degrees of mitral regurgitation. The association between mitral regurgitation and MI with normal coronary arteries remains speculative.

The present study showed a significantly higher cardiac index in group A patients despite the fact that their infarct size, as judged by the magnitude of cardiac enzyme release, was higher than in group B. This may be related to the younger age of the patient and enhanced contractility of the noninfarct zone. Enhanced contractility of the noninfarct zone has been demonstrated in patients with MI with minimal coronary artery disease and has accounted for the well-preserved global left ventricular function in these patients.\(^9\)

Our follow-up data are consistent with those of others in terms of the favorable prognosis of these patients.\(^2,5,8,20\) However, the uniform absence of any mortality or recurrence of MI may be more apparent than real since our study population was limited and no control group was present. The annual death rate and recurrence of MI in such patients have been estimated to be 1.5% and 2.7%, respectively.\(^9\)

**Limitations of the Study**

Owing to the retrospective nature of this study, certain etiologic factors may not have been recognized as they might have been in a prospective trial. Platelet function analysis and rhythm disturbance evaluation could have been obtained had the study been prospective. Echocardiography and contrast-enhanced echocardiography for the detection of embolic sources and patent foramen ovale respectively might have been more uniformly obtained. Two patients were unavailable for follow-up. In addition, a small sample size of both groups may obscure other possible significant differences.

**Conclusions**

This study reports on the prevalence rate, clinical, and hemodynamic profile of 12 patients with MI and angiographically normal coronary arteries. Though a number of reports have addressed this entity previously, there are several features in this study that may be of interest. First, our definition of an insignificant coronary artery lesion has been the strictest definition reported in the literature, i.e., less than 30% stenosis in only one epicardial vessel. This may have accounted for the low prevalence rate of 1% in our patients. Second, there was a bimodal sex and age distribution in the occurrence of this entity: a younger age group, all men, who had Q-wave MI with a larger infarct size yet maintaining a higher cardiac index vs an older group, all women, who had non-Q-wave MI and a lower cardiac index despite having a smaller infarct size. Third, cigarette smoking was significantly higher and uniformly present in group A patients. Fourth, a striking association was noted between this entity and mitral valve abnormalities: four patients had mitral valve prolapse and another six had variable degrees of mitral regurgitation. A mean follow-up of 4 years showed a favorable prognosis in both groups.

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